

AWARD NUMBER: W81XWH-14-1-0568

TITLE: rTMS: A Treatment to Restore Function After Severe TBI

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:

Chicago Association for Research and Education in Science
Hines, IL 60141

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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14. ABSTRACT This study is a double blind randomized placebo-controlled clinical trial using repeated measures . The objective is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. Specific Aims: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.					
15. SUBJECT TERMS Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)					
16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION: The rationale, based on published evidence and pilot data from three subjects, indicate that repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments.

2. KEYWORDS:

Disability Rating Scale (DRS)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative (VS)
Minimally Conscious (MCS)

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Goal 1: Regulatory Requirements (Months 1-4)

Milestones: Local IRB approval and HRPO/ORP approval; 60% completed

Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-4)

Subtask 2a: Hiring and Training of Study Staff

Milestones: Study staff hired and trained at all 3 study sites; 95% completed

Subtask 2b: Development of study related materials and finalize logistics

*Milestones: All study materials and procedures finalized at all 3 study sites; **95% completed***

Major Goal 3: Participant Recruitment, rTMS Intervention and Follow-up (Months 4-32)

*Milestones: All 58 study participants recruited and completion of research participation; **0% completed***

Major Goal 4: Data Analysis (Months 5-36); **0% completed**

What was accomplished under these goals?

For Major Goal 1, Hines' IRB and R&D committee approved the study on 4/20/2015 and 5/26/2015, respectively. Northwestern's IRB approved a study revision on 5/22/2015. The study documents were submitted to Santa Clara Valley Medical Center's IRB and reviewed on 9/11/2015. Their IRB has requested clarifications and changes which will be submitted within the next month. The NU IRB approvals were submitted to HRPO on 6/18/2015 and are pending approval. The Hines IRB approved a revision submitted in June on 7/6/15. This approval was submitted to HRPO on 9/21/2015. On 9/28/2015, Dr. Pape had a discussion with Ms. Roberson at HRPO regarding the changes that HRPO wanted for this study. These changes are being submitted to Hines, Northwestern and SCVMC's IRBs. Once these study changes are approved, they will be resubmitted to HRPO for approval.

For Major Goal 2, all study staff have been hired at all three sites. REDCap has been selected as the study database. We are currently creating the database and piloting the use of electronic data collection forms. Dr. Linda Isaac will be the new site PI at SCVMC. Dr. Isaac will be replacing Dr. Thao Duong who was temporarily SCVMC's site PI when Dr. Stephanie Kolakowsky-Hayner stepped down as site-PI. This paperwork is in process of being submitted.

For Major Goals 3 and 4, we have started finalizing subject recruitment systems at Northwestern, RIC and Hines VA. Once all local IRB and HRPO/PRO approvals are obtained, subject recruitment will begin.

What opportunities for training and professional development has the project provided?

Research staff have been trained to do transcranial magnetic stimulation and neurobehavioral testing.

How were the results disseminated to communities of interest? Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

For the next reporting period, the goals are to obtain SCVMC IRB approval and HRPO/ORP approval. We will begin subject recruitment and screening procedures and have 1-2 subjects enrolled at Hines VA or Northwestern University.

4. **IMPACT:** Nothing to report.
5. **CHANGES/PROBLEMS:** Dr. Linda Isaac has assumed the position of Director of Rehabilitation at Santa Clara Valley Medical Center as of October 2015. Dr. Isaac will assume the position of Collaborating PI at SCVMC for this research project. Therefore, the appropriate paperwork is being submitted to make Dr. Isaac the PI and remove Dr. Duong as the Collaborating PI.
6. **PRODUCTS:** Nothing to Report
7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

What individuals have worked on the project?

Name: Brett Blabas, MS No Change

Name: Lauren Scimeca, MS

Project Role: Research Assistant at Hines VA (RAH)

Nearest person month worked: 3

Contribution to Project: Ms. Scimeca has assisted with the preparation of Hines VA and Northwestern IRB amendments as well as SCVMC's initial IRB submission packet.

Name: Ann Guernon, MS, CCC-SLP, CCRC

Project Role: Clinical Research Coordinator at Hines VA

Nearest person month worked: 3

Contribution to Project: Ms. Guernon has overseen Hines VA and Northwestern IRB amendments as well as SCVMC's initial IRB submission packet. Ms. Guernon has prepared and will continue to prepare all submissions to HRPO and interface with HRPO to address needed amendments.

Name: Theresa Pape, DrPH, MA, CCC-SLP

Project Role: PI

Nearest person month worked: 0.6

Contribution to Project: Dr. Pape has overseen protocol development, staffing at each study site and overall project flow.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following changes have occurred in the active other support of the PI and key personnel:

Pape, Theresa Louise-Bender

New Support

N1416-P (PI-Maheen) 04/14-03/16 .60 Calendar-Contributed

\$200,000

“rTMS to Improve Cognitive Function in Mild to Moderate TBI”

Co-Investigator

VA ORD RR&D Spire

Susan Andrese, MHA

Acting Administrative Officer, Research & Development

Grants Administrator, Research & Development (151)

Bldg. 1, Room C347

Edward Hines Jr. VA Hospital, Hines, IL 60141

Phone: 708) 202-7447 Fax: 708) 202-2684

To assess the efficacy of rTMS in improving executive functioning in Veterans with mild to moderate TBI in order to maximize rehabilitation outcomes.

RX000949-01A2 (Herrold-CDA II Award) 05/14 - 04/19 .24 Calendar-Contributed

\$820,020

Pape-Primary Mentor

“Brain targets for alcohol craving in Veterans with mTBI”

Pape-Primary Mentor

VA RR&D CDA II

Susan Andrese, MHA

Acting Administrative Officer, Research & Development

Grants Administrator, Research & Development (151)

Bldg. 1, Room C347

Edward Hines Jr. VA Hospital, Hines, IL 60141

Phone: 708) 202-7447 Fax: 708) 202-2684

This is a CDA II award where trainee will be characterizing alcohol craving among Veterans with alcohol use disorder, mild TBI, and post-traumatic stress disorder and develop a neurotherapeutic intervention to reduce craving among these Veterans.

W81XWH-14-1-0568 (PI-Pape) 09/14-09/17 3 Calendar-Contributed

\$2,993,848

“rTMS: A Treatment to Restore Function after Severe TBI”

Principal Investigator

USAMRMC/USAMRAA

Science Officer: Jill F. Ciccarello

U.S. Army Medical Research & Materiel Command

Email: Jill.f.ciccarello.ctr@mail.mil Phone: 253-906-3272

The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

The specific aims are to: (1) Determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale; (2) Determine presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function; (3) Examine the effect of rTMS on white fiber tracts and whether or not the

rTMS-related effects correlate with improving neurobehavioral function; (4) Confirm rTMS safety for severe TBI.

MagVenture (PI-Pape) 02/15-01/16 .12 Calendar-Contributed
Pilot Grant
\$20,000
“Neurotherapeutic application of intermittent theta burst stimulation for Mild TBI and PTSD: A Pilot Study”
Principal Investigator
MagVenture
Determine immediate effects of Active APT-III + Active iTBS on outcomes measured as Neuropsychological attention test measures, Functional Measures, Symptom Measures and Neurophysiological Measures between baseline and after 30 treatment sessions. Determine long-term effects of Active APT III+ Active iTBS according to above measures, by computing change between baseline and after follow-up. Determine how effects identified for Objectives 1 & 2 relate to the underlying neurocognitive system of attention.

IK1RX001850 (PI-Kletzel) 06/15-06/17 .24 Calendar-Contributed
\$48,754
“Cognitive Biomarker Targets for Treatment in Veterans with Parkinson's Disease”
Primary Mentor
VA RR&D CDA I
Susan Andrese, MHA
Acting Administrative Officer, Research & Development
Grants Administrator, Research & Development (151)
Bldg. 1, Room C347
Edward Hines Jr. VA Hospital, Hines, IL 60141
Phone: 708) 202-7447 Fax: 708) 202-2684
Characterize cognitive function in a cohort of Veterans with Parkinson's Disease using neuropsychological tests and resting state functional connectivity. Identify a neural therapeutic target for Veterans with PD-MCI.

W81XWH-15-1-0516 (PI-Pape) 09/15-09/19 2.4 Calendar Months
\$2,999,030
“Neuromodulation and Neurorehabilitation for Treatment of Functional Deficits after mTBI + PTSD”
Principal Investigator
USAMRMC/USAMRAA
DoD, Defense Medical R&D Program, Psychological Health/Traumatic Brain Injury Research Program, Congressionally Directed Medical Research Programs, Clinical and Rehabilitative Medicine Research Program/Joint Program Committee 8, Neurosensory and Rehabilitation Research Award
Sandra Rosario
U.S. Army Medical Research Acquisition Activity
Grant Specialist - Assistance Agreements A-1 Team

843 Chandler Street

Fort Detrick, MD 21740

Email: sandra.rosario2.civ@mail.mil; Phone #301-619-4063

Aim I will determine immediate effects of Active APT-III + Active iTBS on neuropsychological measures of attention, measures of function and symptoms between baseline and endpoint. Aim II will determine sustainability and long-term of effects of Active APT III+ Active iTBS for neuropsychological, symptom and functional outcome measures, by comparing endpoint and 10-week post-treatment follow up. Aim III will determine how effects identified for Aims 1 & 2 relate to the underlying neurocognitive system of attention by examining the relationship between the functional and structural connectivity of the attention networks with the neuropsychological, functional and symptoms outcomes. Aim IV addresses the need to confirm safety of iTBS in this population.

Bhaumik, Dulal Kumar

New Support

Title: Center for Alcohol Research in Epigenetics

Source of Support: NIAAA/NIH (PI-S Pandey)

Period: 2015-2019, Role: Co-I (5%)

Description: Alcoholism is a major public health concern worldwide. These novel studies and important collaborations among this exemplary research team will increase our understanding of the epigenetic mechanisms that may be involved in the pathophysiology of alcoholism. Ultimately, these studies may lead to the identification of epigenetic targets, which can be used to develop new pharmacotherapies to treat or prevent alcoholism.

Title: Interactive Virtual Training (IVT) for Early Career Teachers in Urban Schools

Source of Support: Institute of Education Sciences, (PI: Shrenoff)

Period: 02/01/115-01/31/19 Role: Co-PI (5%)

Description: The study proposes to develop, iteratively refine, and pilot test the Interactive Virtual Training (IVT) system designed to enhance and accelerate ECTs' use of evidence-based behavior management practices with students at risk for developing serious behavior problems by providing opportunities for: (1) Reflection and Problem Solving, and (2) Practice with Feedback.

Title: Myelin markers and modifiable risks of vascular aging in African Americans

Source of Support: National Institute on Aging, R21 AG048176

Period: 9/1/15-3/31/17 Role: Co-I (5%)

Description: We will combine state-of-the-art neuroimaging, including myelin mapping, with geospatial coding of neighborhood health to determine modifiable risks of vascular brain aging. Lamar serves at PI.

Title: Neuromodulation and Neurorehabilitation for Treatment of Functional Deficits after mTBI plus PTSD

Source of Support: Department of Defense MR141205 (PI: Pape)

Period: 2015-2018 Role: Co-I (15%)

Description: I will use mixed-effects model to analyze data, will study correlation between neuro connectivity and neuro behavioral data. Multiple comparisons will be addressed to control false discovery rates.

Parrish, Todd

New Support

U01 DK082342 (PI: Schaeffer/Klumpp)

09/15/08 – 6/30/16

0.6 calendar months

NIH/NID

\$232,099

Dr. Christopher Mullins

DIVISION KIDNEY, UROLOGIC, & HEMATOLOGIC DISEASES

NIDDK, National Institutes of Health

Building 2DEM, Room 637

6707 Democracy Blvd.

Bethesda, MD 20892-5458

“Interactive Mechanisms of Pelvic Pain”

Major Goals: The goal is to study the effect of chronic pain on the brain. My role is to supervise data collection and quality control for the whole multi-center study.

Aims: We will study mechanisms of SCPP in three innovative and synergistic projects. In Project I, we identify novel brain biomarkers of SCPP by characterizing brain morphometry/activity and cognitive function. In Project II, we will exploit the NIH Roadmap initiative PROMIS to determine the prevalence of SCPP in a large cohort. Finally, in Project III, we dissect pelvic organ crosstalk and spinal cord integration mechanisms that mediate co-morbidities and sustained pain in SCPP murine models. By focusing on the bladder, prostate, and bowel, our studies will benefit equally digestive disease and kidney/urologic disease, the dual missions of NIDDK, and provide the critical foundation for targeted therapies for SCPP.

P50 DC012283 (Thompson)

04/01/13-03/31/18

3.00 calendar months

NIH/P50

\$380,492 (Core B)

“Neurobiology of Language Recovery in Aphasia: Natural History and Treatment-Induced”

Grants Management Specialist:

Hoai Doan

GRANTS MANAGEMENT BRANCH

Bldg EPS, Rm 400B

Mail Stop 7180

Bethesda, MD 20892-2320

Hoaid@nidcd.nih.gov

Major Goals: The goal of this project is to assess treatment effects of language recovery in aphasic participants using behavioral and neuroimaging data.

Specific Aims:

There are two overarching aims of this large-scale study.

1. The first is to examine the impact of domain-specific treatment on language and brain functions in people with chronic aphasia. At the same time the natural history of language recovery and associated language and brain functions will be studied in untreated chronic aphasia. For both aphasic groups, immediate and long-term neural and cognitive changes (6 month and one year assessments) will be evaluated based on:

- Language measures, within and across language domains, and
- Neurobiological measures, including
 - BOLD signal during domain-specific and cross-project fMRI tasks
 - HRF time-to-peak (TTP)
 - Level of perfusion in non-infarcted cortical tissue
 - Resting state connectivity (i.e., language and other networks)
 - White matter connectivity (using DTI) between language areas and across hemispheres

2. The second aim of the project is to evaluate a set of neural and behavioral variables for their potential to predict language and brain recovery (i.e., we will seek to identify bio and behavioral markers):

- Biological and social predictors: age, education level
- Language and cognitive predictors: domain-specific language ability, overall language severity (i.e., WAB AQ), and learning ability (explicit/declarative and implicit/procedural memory)
- Neurobiological predictors
 - Structural lesion volume, cortical thickness, and location
 - HRF time-to-peak (TTP)
 - Level of perfusion in non-infarcted cortical tissue
 - Resting state connectivity (i.e., language and other networks)
 - White matter connectivity (using DTI) between language areas and across hemispheres

R01DE022746-02S1 (Apkarian)

7/30/12-6/30/17

0.55 calendar months

NIH/NINDS

\$459,328

“Cortico-striatal plasticity in the transition to chronic pain”

Mr. Kevin Crist

Grants Management Specialist

kc281u@nih.gov

The starting point of this grant is a reverse translational step where we unravel cellular and molecular mechanisms in rodents for a brain circuit that predicts transition to chronic pain in humans. The results of the mechanistic studies are then used to identify potential therapeutic drugs, first tested in rodents and then translated to the clinical setting. If successful, it will be the first demonstration that human brain imaging coupled with

surrogate animal models for chronic pain can dramatically advance both the basic science and the clinical prevention of the transition from acute to chronic pain.

Specific Aims:

Aim 1. To determine how the properties of nucleus accumbens (NAc) spiny projection neurons (SPNs) expressing dopamine (DA) 1 or 2 receptors (DR1 or DR2), and their linkage to prefrontal cortex and limbic structures, are altered during the transition from nerve injury to chronic pain-like behavior in rodents.

Aim 2. To determine if pharmacological agents that attenuate the adaptations in the corticostriatal circuit can prevent the induction of the chronic pain state.

Aim 3. In a clinical trial coupled with functional imaging, therapeutic efficacy of a drug is tested for preventing transition to chronic back pain.

1R01AT007987-01A1 (Apkarian)

09/30/2013-05/31/2018

0.6 calendar months

“Brain mechanisms for clinical placebo in chronic pain” \$692,803

Grants Management Specialist:

John R. Glowa

6707 Democracy Blvd. II, Suite 401

Bethesda, MD 20892

This project is designed to examine brain properties for placebo responses in chronic back pain patients.

Specific Aims:

1.) Determine in chronic pain patients that the propensity for placebo responses in RCTs is: 1)

predictable by brain biomarkers, and 2) reproducible within individuals with chronic back pain (CBP).

2.) Evaluate the interaction between placebo response and medication treatment.

3) Develop an algorithm that serves as a self-report measurement tool for predicting propensity to placebo (TOPPP).

1R01HD079076-01A1 (Elliott)

09/01/2014-05/31/2019

0.6 calendar months

NIH R01

\$250,000

“Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries”

Grants Management Specialist

Diana Hong

301-435-6997

hongdi@mail.nih.gov

Motor vehicle-related injuries resulting in whiplash-associated disorders (WAD) send more than 4 million people to hospital emergency departments every year in the United States with associated healthcare costs estimated to be a staggering \$100 billion. Current treatments consisting of medications, physical therapy, education, and assurance are helpful to the vast majority of individuals with whiplash, but do not, for unknown reasons, work for all patients. Therefore, there is a vital need to develop more clinically effective assessments, such as the one studied in this project, for accurately identifying,

and treating, those at risk of developing chronic WAD to reduce the societal and personal burden of this debilitating condition

Specific Aims:

AIM 1: To test the hypothesis that the time course of fatty infiltrates in the neck and leg muscles

predicts the course of chronic WAD.

AIM 2: To provide the first objective MRI evidence that mild spinal cord injury occurs in whiplash

and predicts the course of chronic WAD.

AIM 3: To determine the extent to which volitional muscle activation deficiencies and muscle fatigue

in the lower extremity correlates with chronic WAD disability.

CDMRP USAMRAA PT1302741 (Rosenow)

09/01/2014-09/29/2017

0.6 calendar months

DOD Subcontract from Chicago Association for Research and Education in Science

rTMS: A Treatment to Restore Function after Severe TBI” \$46,655

Grants Management Specialist:

Cindy Reutzell, Executive Director

The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

Specific Aims:

(1) Determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale

(2) Determine presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function

(3) Examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function; (4) Confirm rTMS safety for severe TBI.

R01MH100117-01A1 (Nusslock)

12/01/2014-01/31/2019

0.79 calendar months

NIH

\$249,971

Symptom Dimensions of Threat-and Reward-Related Neurocircuitry

This grant examines the commonalities and differences in threat and reward-related neural circuitry underlying the hierarchical structure of depressive and anxiety symptoms.

Pape-VA CDMRP//W81XWH-14-1-0568 (Pape)

10/01/2014-09/30/2017

0.6 calendar months

DOD Subcontract from Chicago Association for Research and Education in Science

\$46,655

“rTMS: A Treatment to Restore Function after Severe TBI”

The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

R01 AG045571-01 (Rogalski Miller)

04/01/2015-03/31/2020

0.12 calendar months

NIH

\$426,565

Grants Management Specialist:

Ryan Blakeney

blakeneyr@mail.nih.gov

301-451-9802

“Exceptional Cognitive Aging: Neuropsychologic, Anatomic and Pathologic Correlates”

The proposed research will characterize, in a comprehensive, interdisciplinary and longitudinal manner, a cohort of octo- and nonagenarians who display unusually successful cognitive aging and whom we have termed SuperAgers. The investigation of this population of elderly has not received extensive experimental attention. Identification of neurobiologic features that contribute to exceptionally successful cognitive aging may make it possible to help elderly avoid disease and disability, improve quality of life and alleviate a looming public health crisis.

Specific Aims:

Aim 1: Establish the longitudinal phenotype of SuperAgers through neuropsychological performance, structural MRI and amyloid PET imaging.

Aim 2: Investigate the prevalence and density of age-related plaque and tangle accumulation, status of basal forebrain cholinergic system and neuronal number in SuperAgers

Aim 3. Establish a resource of behavioral and biological data for further resource sharing and collaborative investigations of SuperAgers.

R01DK100924-01 (Apkarian)

09/24/2013-09/26/2016

0.24 calendar months

NIH

\$386,250

Brain imaging based strategies for treating UCPPS pain

Grant Management Specialist:

Carolyn Kofa

kofac@extra.niddk.nih.gov

301-594-7687

Major goals: The overall goal is to demonstrate increased power, sensitivity, and objectivity for a double blind randomized clinical trial when it is combined with brain imaging and coupled with frequent assessment when determining treatment efficacy for urological pain of UCPPS.

Specific Aims:

Aim 1: Evaluate differential efficacy for UCPPS urological pain relief between placebo and DCS.

Aim 2: Evaluate differential brain functional biomarkers for treatment response and treatment propensity, for placebo and for DCS.

Aim 3: Demonstrate that brain morphology renormalizes in treatment responders. Given the financial and time constraints of this RFA, the study is powered to be a proof of concept and to demonstrate the strength of the methodology in providing objective evidence for individualized treatment choices when evaluating novel therapies in UCPPS.

Ripley, David L.

Completed Support

Colorado Traumatic Brain Injury Trust 7/1/2010 – 6/30/2015
Investigator
\$1,125,000 (total award)
Neuroendocrine Dysfunction Following TBI: The effects of Testosterone Replacement

Rosenow, Joshua

New Support

Title: Spatiotemporal Mechanisms of Olfactory Processing in the Human Brain
Grant Number: R01DC013243 (PI: Gottfried)
Role: Co-Investigator
Time Commitment: 0.36 calendar months
Supporting Agency: National Institute on Deafness and Other Communication Disorders
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Susan Sullivan, Division of Scientific Programs, Bldg NSC, Rm 8323, Mail Stop 9670, 31 Center Drive, Bethesda, MD USA 20892-2320
Performance Period: 06/15/2013 – 05/31/2018
Current Year Direct Costs: \$174,857
Brief Description of the Project's Goals: The major aim of this project is to use intracranial EEG techniques to investigate the basic electrophysiology of the human olfactory system in patients with medically resistant epilepsy.
Specific Aims: Aim 1: Characterizing the time-frequency dynamics of odor coding and categorization. Aim 2: Characterizing the spectral content of odor information across and between sniffs. Aim 3: Characterizing the spatiotemporal evolution of odor perception in a single sniff.

Title: Amantadine + rTMS as a Neurotherapeutic for Disordered Consciousness after TBI
Grant Number: R21HD075192 (PI: Pape)
Role: Co-Investigator
Time Commitment: 0.36 calendar months
Supporting Agency: NIH Subcontract from Chicago Association for Research and Education in Science
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Mary Ellen Michel, 6100 Executive Blvd Room 2A03, Bethesda MD 20892
Performance Period: 08/05/2013-07/31/2016 (NCE)
Current Year Direct Costs: N/A

Brief Description of the Project's Goals: The project's research objective is to examine the safety and efficacy of repetitive transcranial magnetic stimulation (rTMS) combined with Amantadine (TMS + Amantadine) relative to rTMS Alone and Amantadine Alone for persons in chronic states of seriously impaired consciousness.

Specific Aims: The specific aims are to: (1) Demonstrate that rTMS+Amantadine is safely tolerated, (2) Determine neurobehavioral effect of rTMS+Amantadine, and (3)

Characterize pre-and post-treatment neural changes in neural. Aim 1 is based on our preliminary safety data and safety data regarding Amantadine.

Title: rTMS: A Treatment To Restore Function After Severe TBI

Grant Number: CDMRP USAMRAA PT1302741 (PI: Pape)

Role: Co-Investigator

Time Commitment: 1.2 calendar months

Supporting Agency: DOD Subcontract from Chicago Association for Research and Education in Science

Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Cindy Reutzel, Executive Director, Building One, Room C303, 5000 S. 5th Avenue, Hines, IL 60141

Performance Period: 10/1/14 - 9/30/17

Current Year Direct Costs: \$54,551

Brief Description of the Project's Goals: The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

Specific Aims: (1) Determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale; (2) Determine presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function; (3) Examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function; (4) Confirm rTMS safety for severe TBI.

Title: RELIEF: A Global Registry to Evaluate Long-Term Effectiveness of Neurostimulation Therapy for Pain

Grant Number: Protocol #A7007 (Site PI: Rosenow)

Role: Site Principal Investigator

Time Commitment: 0.12 calendar months

Supporting Agency: Boston Scientific Corporation

Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Ann Masuda, Boston Scientific, 25155 Rye Canyon Loop, Valencia, CA 91355

Performance Period: 10/01/2013-open

Current Year Direct Costs: Per Patient Reimbursement

Brief Description of the Project's Goals: The primary purpose of the clinical study is to better understand the long-term results of chronic back and leg pain patients treated with a Boston Scientific neurostimulation system.

Specific Aims: The primary objective is to compile characteristics of real-world clinical outcomes for Boston Scientific commercially approved neurostimulation systems for pain in routine clinical practice, when used according to the applicable Directions for Use

Title: PRO (Precision Retrospective Outcomes) Study

Grant Number: Protocol #A7005 (Site PI: Rosenow)

Role: Site Principal Investigator

Time Commitment: 0.12 calendar months

Supporting Agency: Boston Scientific Corporation

Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Laura Denver, Boston Scientific, 25155 Rye Canyon Loop, Valencia, CA 91355

Performance Period: 07/01/2014-open

Current Year Direct Costs: Per Patient Reimbursement

Brief Description of the Project's Goals: This study will evaluate deidentified (anonymous) data in subject medical charts to review the clinical outcomes of spinal cord stimulation.

Specific Aims: The primary objective of this study is to characterize real-world clinical outcomes of spinal cord stimulation (SCS) using retrospective review of de-identified patient records.

Title: INTREPID Study: Implantable Neurostimulator for the Treatment of Parkinson's Disease

Grant Number: Protocol #A5002 (Site PI: Rosenow)

Role: Site Principal Investigator

Time Commitment: 0.12 calendar months

Supporting Agency: Boston Scientific Corporation

Name and Address of the Funding Agency's Procuring Contracting/Grants Officer: Alexander Chernyak, Boston Scientific, 25155 Rye Canyon Loop, Valencia, CA 91355

Performance Period: 11/01/2014-open

Current Year Direct Costs: Per Patient Reimbursement

Brief Description of the Project's Goals: To evaluate the safety and effectiveness of the Boston Scientific implantable deep brain stimulation (DBS) Vercise™ system for bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy for improving the number of waking hours per day with good symptom control and no troublesome dyskinesia (ON time) in adults with advanced, levodopa-responsive bilateral Parkinson's disease (PD) which is not adequately controlled with medication.

Specific Aims: Primary Outcome Measures: improvement in ON time as measured by Parkinson's disease diary and the difference in the mean change from baseline to 12 weeks post-randomization between the active and control groups in the ON time as measured by Parkinson's diary.

Wang, Xue

New Support

CDMRP USAMRAA PT1302741 (Rosenow) 09/30/14-09/29/17 1.2 calendar months

DOD Sub from Chicago Association for Research and Education in Science
\$46,655

“rTMS: A Treatment to Restore Function after Severe TBI”

The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

Grants Management Specialist:

Cindy Reutzel, Executive Director

The purpose of this study is to determine the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS) for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI.

Specific Aims:

(1) Determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale

(2) Determine presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function

(3) Examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function; (4) Confirm rTMS safety for severe TBI.

Isaac, Linda

Dr. Isaac’s other support is in the process of submission for review by Contracts Specialist

What other organizations were involved as partners?

Organization Name: Northwestern University

Location of Organization: Chicago, IL, USA

Partner’s Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center

Location of Organization: San Jose, CA, USA

Partner’s Contribution to the Project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES: None

QUAD CHARTS: See attached Quad Chart.

rTMS: A Treatment to Restore Function after Severe TBI

PT130274

W81XWH-14-1-0568



PI: Theresa Pape, DrPH

Org: Chicago Association for Research and Education in Science (CARES)

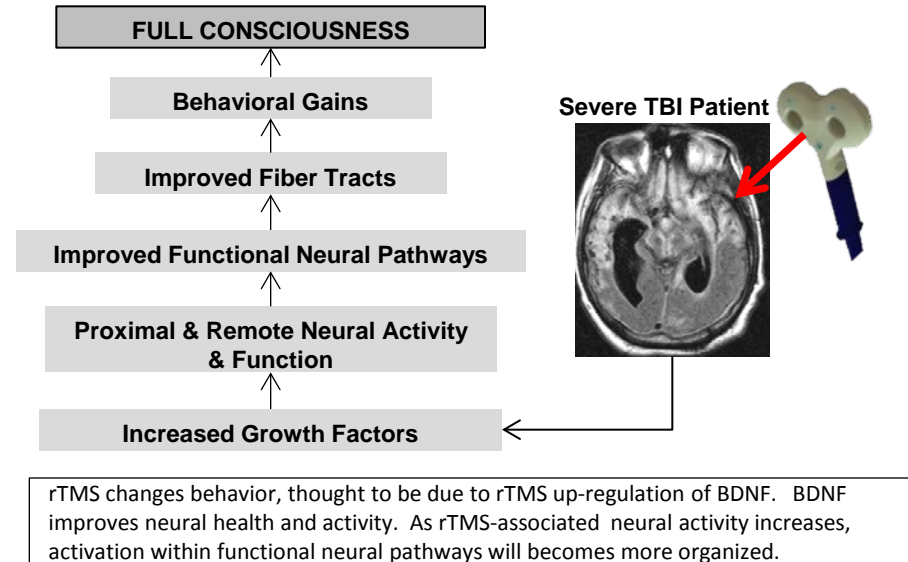
Award Amount: \$2,993,848

Study Aims

1. Determine safety of repetitive Transcranial Magnetic Stimulation (rTMS) for severe TBI.
2. Determine if rTMS is related to improved neurobehavioral functioning during rTMS and during the 3 week follow up after stopping rTMS.
3. Determine whether rTMS associated changes in functional neural activation to auditory stimuli correspond with activation in higher order brain regions.
4. Determine whether rTMS is related to changes in white fiber tracts directly under and remote from site of stimulation.

Approach

To address the need for robust treatments that safely induce and modulate neural activity and result in improved functional recovery for severe TBI, we propose a double blind randomized sham controlled clinical trial.



Timeline and Cost

Activities	CY	14	15	16	17
FDA & IRB Revisions, Contracts					
Subject Enrollment & Data Collection					
Data Entry, Processing & Analyses					
Estimated Budget (\$3,000,000)					

Goals/Milestones (Example)

CY14 Goal – Study Start-Up

- ☐ Obtain local IRB and HRPO approval
- ☒ Obtain FDA IDE approval

CY15 Goals – Participant Recruitment & Enrollment of 17 subjects

- ☐ Enroll 7 subjects at SCVMC & 10 at NU/Hines VA
- ☐ Database Entry for all 17 subjects

CY16 Goals – Enrollment of 32 subjects

- ☐ Enroll 16 subjects at SCVMC & 16 at NU/Hines VA
- ☐ Database Entry for all 32 subjects

CY17 Goal – Enrollment of 10 Subjects and Complete Data Analysis

- ☐ Enroll 7 subjects at SCVMC & 3 at NU/Hines VA
- ☐ Complete Analyses

Comments/Challenges/Issues/Concerns

- Funding awarded 9/30/2014 so timeline has shifted accordingly

Budget Expenditure to Date

Projected Expenditure: \$357,240

Actual Expenditure: \$357,240

Updated: 9/30/2015